EFFECTS OF PULSATILE VERSUS NONPULSATILE FLOW ON CEREBRAL HEMODYNAMICS DURING PEDIATRIC CARDIOPULMONARY BYPASS WITH DEEP HYPOTHERMIC CIRCULATORY ARREST

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***Abstract*- Cardiopulmonary bypass (CPB) with total circulatory arrest (TCA) adversely affects the neurologic outcome of pediatric patients after cardiac surgery. This study is designed to determine the effects of pulsatile versus nonpulsatile perfusion on regional and global cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), cerebral oxygen delivery (CDO_2), and cerebral vascular resistance (CVR) before and after TCA in a neonatal piglet model. Twelve piglets were used in pulsatile (n = 6) and nonpulsatile (n = 6) groups. All piglets underwent 60 minutes of TCA and 45 minutes of rewarming. CBF, $CMRO_2$, CDO_2, and CVR were determined before TCA at a cerebral perfusion pressure (CPP) of 55 mmHg, and after TCA at CPP's of 55, 40, and 70 mmHg. Pulsatile flow increased regional and global CBF, $CMRO_2$, and CDO_2, and decreased CVR compared to nonpulsatile perfusion at all experimental stages. However, CBF, $CMRO_2$, CDO_2, and CVR diminished after TCA in both groups. These results suggest that the use of pulsatile flow improves cerebral recovery after TCA, and thus it may minimize brain injury compared to nonpulsatile flow in neonates and infants. Our results also confirm that TCA is the major cause for cerebral dysfunction during CPB.**

***Index Terms*–Pulsatile flow, cerebral hemodynamics, cardiopulmonary bypass, deep hypothermic circulatory arrest, neonates and infants**

I. INTRODUCTION

Complex congenital heart defects can be routinely repaired using extreme techniques such as deep hypothermic cardiopulmonary bypass (DHCPB) with total circulatory arrest (TCA). During TCA, there is no blood flow to any organs, and hypothermia is the only protection for organ recovery. During the past two decades, the mortality rate after DHCPB was significantly reduced but morbidity, especially brain injury, is still a challenging clinical problem [1-4]. Several investigators have shown that cerebral blood flow and cerebral metabolism diminishes after TCA in neonates and infants [4-9]. Although the mechanisms of brain injury have not yet been fully understood, techniques, which enhance cerebral blood flow and metabolism, may minimize the brain injury [9].

Controversy over the benefits of pulsatile perfusion during pediatric CPB continues, and only 6 percent of all pediatric centers in the United States use pulsatile flow [10]. However, we have demonstrated that pulsatile flow after TCA may minimize injury on vital organs in a neonatal piglet model [11].

The objective of this study was to investigate the effects of pulsatile versus conventional nonpulsatile perfusion on cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), cerebral oxygen delivery (CDO_2), and cerebral vascular resistance (CVR) at different cerebral perfusion pressures (CPP) before and after TCA in a neonatal piglet model. The authors hypothesize that the use of pulsatile flow may improve cerebral recovery before and after TCA.

II. METHODOLOGY

Twelve piglets, with a mean weight 3 kg, were used in pulsatile (n=6) and nonpulsatile (n=6) groups. All animals received humane care as described in the "Guide for the Care and Use of Laboratory Animals" of the National Academy of Sciences, published by the National Institute of Health (NIH Publication No. 85-23, 1985).

A. Anesthesia / Surgery

Animals were premedicated with intramuscular ketamine hydrochloride (20 mg/kg), acepromazine maleate (1 mg/kg), and intravenous methylprednisolone (40 mg/kg). After endotracheal intubation and establisment of an intravenous line, intravenous boluses of fentanyl (100 µg/kg) and pancuronium bromide (0.3 mg/kg) were given, and mechanical ventilation was begun with an infant pressure-cycled ventilator (Sechrist Industries, Anaheim, CA). Anesthesia was maintained with a fentanyl infusion (100 µg/kg/hr). A nasopharyngeal temperature probe was inserted (Model 431D, Yellow Prings, Inc., OH). Two separate burr holes were made over the superior sagittal sinus. The holes were 1cm. apart. A 3 French Millar micromanometer (Millar Instruments, Inc., Houston, TX) was inserted into the superior sagittal sinus for monitoring the sagittal sinus venous pressure. The other burr hole was used for sagittal sinus

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venous blood sampling. After a median sternotomy was performed, the ascending aorta and the right atrium were cannulated with a 10 French aortic cannula and a 18-21 French venous cannula, respectively. The CPB circuit included a membrane oxygenator with heat exchanger (Cobe VPCML Plus, Cobe Cardiovascular, Inc., Arvada, CO), and either a conventional nonpulsatile roller pump (Stöckert-Shiley, Irvine, CA) for the nonpulsatile experiments or the neonate/infant pulsatile pump for the pulsatile studies [12]. The CPB circuit was primed with heparinized fresh blood and Lactated Ringer's solution. Hematocrit was maintained at 22% to 24% during CPB. The gas mixture was adjusted and sodium bicarbonate was added to obtain a normal blood gas.

B. Experimental Design

After initiation of CPB with a pump flow rate of 150ml/kg/min, all piglets underwent normothermic CPB for 15 minutes, then hypothermia was induced by core cooling with a heat exchanger to 18^{o}C for 20 minutes, followed by DHCA for 60 minutes, and rewarming with a pump flow rate of 150ml/kg/min for 45 minutes.

CBF was determined using a radiolabelled microsphere technique, and $CMRO_2$, CDO_2, and CVR were calculated during CPB prior to DHCA (37^{o}C) at a cerebral perfusion pressure of 55mmHg (pre-55), and after TCA at CPP's of 40 (post-40), 55 (post-55), and 70 mmHg (post-70). Cerebral perfusion pressure was controlled by adjusting the pump flow rate. During cooling and rewarming, alpha-stat acid-base technique was used. This technique maintains pH at 7.4 and $PaCO_2$ at 35 to 40 mmHg.

The following formulas are used to calculate CBF, $CMRO_2$, CDO_2, CVR, and CPP.

$$CBF = Qrb \times (Ct/Crb) \times (100/Wt) \quad (1)$$

CBF = Cerebral blood flow (ml/100gm/min)
Qrb = Rate of reference sample withdrawal (ml/min)
Ct = Total number of microspheres in the organ per minute
Wt = Total weight of the tissue (gm)

$$CMRO_2 = CBF \times (CAO_2 - CSSO_2) \quad (2)$$

$CMRO_2$ = Cerebral metabolic rate of oxygen (ml/100gm/min)
CAO_2 = Arterial Oxygen Content
$CSSO_2$ = Sagittal sinus oxygen content

$$CDO_2 = CBF \times CAO_2 \quad (3)$$

CDO_2 = Cerebral oxygen delivery (ml/100gm/min)

$$CVR = (MAP - SSVP) / CBF \quad (4)$$

CVR = Cerebral vascular resistance (mmHg.100gm.min/ml)
MAP = Mean arterial pressure (mmHg)
SSVP = Sagittal sinus venous pressure (mmHg)

$$CPP = MAP - SSVP \quad (5)$$

CPP = Cerebral perfusion pressure (mmHg)

C. Microsphere Injection

All injection of microspheres (Tin-113, Ruthenium-103, Niobium-95, Scandium-46) were made into a side port of arterial tubing 30 cm proximal to the aortic cannula while the animal was maintained at normothermia. Before the injection of microspheres, a SWP Vortex Mixer (baxter Healthcare Corp., McGaw Park, IL) was used to agitate the microsphere vial vigorously for 2 minutes. Then in order to break up the aggregations, the vial was sonicated in warm water for 10 minutes (Sonicator, Model 8850, Cole-Parmer instrument Co., Chicago, IL). After this process, the vial was agitated for another minute. Then, 1 ml of microsphere suspension (approximately 1 million microspheres) was withdrawn into a syringe for injection. A reference blood sample was obtained by means of the femoral arterial catheter. The reference blood sample was withdrawn into a 10 ml syringe with a constant rate of 3 ml/min using a Harvard syringe pump (Harvard Apparatus, South Natick, MA) in a period of 2 minutes.

D. Statistical Analysis

The two-sided ANOVA with repeated measures was used for statistical analysis between pulsatile and nonpulsatile groups at four different stages. A p value less than 0.05 was considered statistically significant. All results were expressed as mean ± standard error of mean (SEM).

III. RESULTS

There were no significant differences between the pulsatile and nonpulsatile groups in arterial pressure, temperature, arterial oxygen tension, arterial carbon dioxide tension, and hematocrit at any of the experimental stages.

A. Global and Regional Cerebral Blood Flow

Global CBF was significantly higher in the pulsatile group compared to the nonpulsatile group before TCA at 55 mmHg (pre-55), and after TCA at 55 mmHg (post-55) and 70 mmHg (post-70). A detailed analysis of global CBF is shown in the Figure 1. Blood flow in the cerebellum, basal ganglia, brain stem, and right and left hemispheres resembled global cerebral blood flow (see Table I).

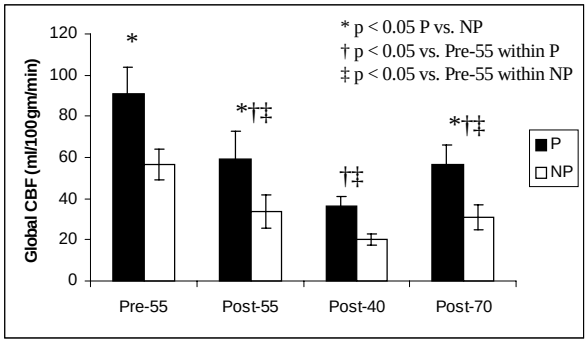

Fig. 1. Global cerebral blood flow

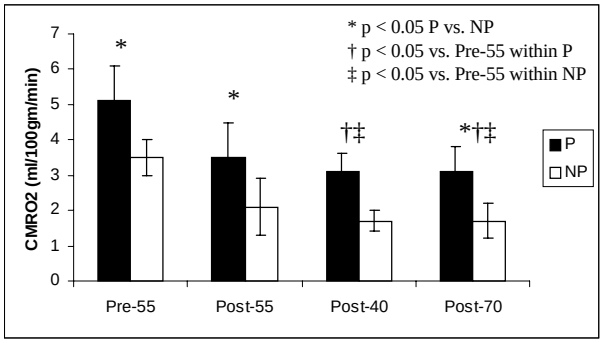

Fig. 2. Cerebral metabolic rate of oxygen

TABLE I
REGIONAL CEREBRAL BLOOD FLOW RESULTS

		Pre-55	Post-55	Post-40	Post-70
Cerebellum	**P**	*100.6±13.9	*111.2±26.5	†59.6±6.2	*104±18.8
	NP	62.3±9.3	60.8±13.7	‡33.2±4	56.3±9.8
Basal Ganglia	**P**	*92.8±14.8	*72.2±18	*†51.8±6.5	*†60.5±12
	NP	54.8±7.2	34.9±8.7	‡25±4	‡31.1±5.7
Brain Stem	**P**	*77.7±15.3	*†55.3±12	*†45.2±6	*†46.7±8.8
	NP	42.1±5.6	29.8±7.4	23.6±3.6	26.4±5.3
Right Hemisphere	**P**	*91.1±12.6	*†50.4±11.2	†30±4.4	*†48.7±7.9
	NP	59.1±7.6	‡28.9±7.1	‡17.5±2.5	‡27.8±5.7
Left Hemisphere	**P**	*89.2±11.8	*†49.4±10.9	†30.4±4.4	*†49.2±8
	NP	55.7±7.8	‡30.3±8	‡17.8±2.4	‡26.9±5.6

*p < 0.05 P vs. NP; † p < 0.05 vs. Pre-55 within P;
‡ p < 0.05 vs. Pre-55 within NP; P = Pulsatile; NP = Nonpulsatile

B. Cerebral Metabolic Rate of Oxygen

Pulsatile flow improved the $CMRO_2$ before TCA at CPP of 55mmHg (pre-55), and after TCA at CPP of 55 mmHg (post-55) and 70 mmHg (post-70) (Fig. 2).

C. Cerebral Oxygen Delivery

The degree of CDO_2 was significantly higher in the pulsatile group than in the nonpulsatile group at all four experimental stages (Fig. 3).

D. *Cerebral Vascular Resistance*

Pulsatile flow significantly decreased the CVR compared to the nonpulsatile flow at all experimental stages (Fig. 4).

IV. DISCUSSION

These results clearly suggest that pulsatile flow significantly increased CBF, $CMRO_2$, CDO_2, and decreased CVR before and after TCA compared to the conventional nonpulsatile flow at all experimental stages. After TCA, global CBF diminished compared to the pre-TCA in both pulsatile and nonpulsatile groups. These results confirmed that TCA is the major cause for cerebral injury after cardiac surgery. However, there were no differences in global CBF results between the pulsatile group after TCA at CPP of 55 mmHg and the nonpulsatile group pre-TCA at CPP of 55 mmHg (Baseline). In other words, pulsatile perfusion after 60 minutes of total circulatory arrest maintained the same level of global cerebral blood flow as nonpulsatile perfusion at pre-TCA. Blood flow in the cerebellum, basal ganglia, brain stem, and right and left hemispheres resembled global cerebral blood flow. There were no differences in $CMRO_2$ levels between the pulsatile group at post-55 and the nonpulsatile group at pre-55. The levels of CDO2 had a similar pattern as CBF and $CMRO_2$ results at the same experimental stages. These results clearly suggest that 60 minutes of total circulatory arrest had minimal adverse effect on the cerebral hemodynamics in the pulsatile group compared to the nonpulsatile group.

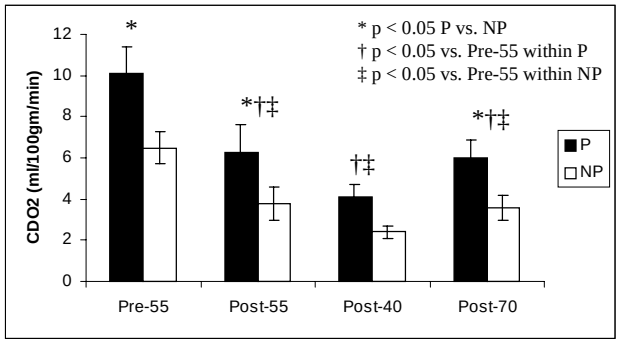

Fig. 3. Cerebral oxygen delivery

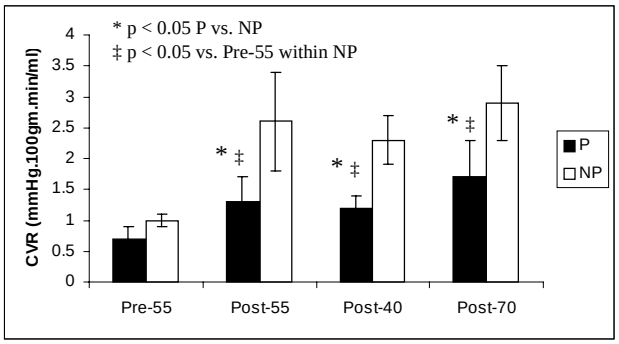

Fig. 4. Cerebral vascular resistance

Previously, we have shown that flat-sheet membrane oxygenators used in this study dampen the pulsatile flow more than hollow-fiber membrane oxygenators [9,13,14]. Despite this limitation, we have documented that the morphology (shape and size) of pulsatile flow generated by this particular pump is more physiologic than conventional nonpulsatile flow [9,13,14].

V. Conclusion

In summary, pulsatile perfusion improves regional and global CBF, $CMRO_2$, and CDO_2, and decreases CVR compared to conventional non-pulsatile perfusion at all experimental stages in this model. However, total circulatory arrest diminishes CBF, $CMRO_2$, and CDO_2 regardless of the perfusion mode. There were no differences in the levels of CBF, $CMRO_2$, and CDO_2 between the pulsatile group at post-55, and the nonpulsatile group at pre-55. Therefore, the use of pulsatile flow may minimize brain injury after deep hypothermic CPB with TCA in pediatric cardiac surgery patients.

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